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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/621,803 | 07/17/2003 | Kenneth A. Browne | GP131-03.UT | 5941 |

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| EXAMINER | |
|---|---|
| STRZELECKA, TERESA E | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1637 | |

DATE MAILED: 10/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/621,803 | BROWNE, KENNETH A. | |
| | Examiner | Art Unit | |
| | Teresa E. Strzelecka | 1637 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *17 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *44-53* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *44-53* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Continued Examination Under 37 CFR 1.114*

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 17, 2006 has been entered.

2. Applicant cancelled claims 1-7, 9, 19, 32, 35 and 38-43 and added new claims 44-53.

3. Applicant's claim cancellations overcame the following rejections: rejection of claims 1-6, 19, 32, 35, 38 and 39 under 35 U.S.C. 102(b) as anticipated by Adams et a.; rejection of claim 7 under 35 U.S.C. 103(a) over Adams et al. and Whitcombe et al; rejection of claims 9 and 40-42 under 35 U.S.C. 103(a) over Adams et al. and Mueller et al.; rejection of claim 43 under 35 U.S.C. 103(a) over Adams et al., Mueller et al. and Gerard et al.

4. Applicant's arguments are moot in view of the new grounds for rejection.

### *Claim Rejections - 35 USC § 103*

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 44-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al. (U.S. patent No. 6,060,288 A; cited in the previous office action), Whitcombe et al. (Nature Biotechn., vol. 17, pp. 804-807, 1999; cited in the previous office action) and Mueller et al. (Histochem. Cell Biol., vol. 108, pp. 431–437, 1997; cited in the previous office action).

A) Regarding claim 44, Adams et al. teach a device for detecting a target nucleic acid, the device comprising:

a solid support bead having a surface (Adams et al. teach a device for amplifying nucleic acids comprising beads (Fig. 1; col. 6, lines 65-67; col. 7, lines 41, 42).);

an amplification primer immobilized to the surface of said solid support bead, said amplification primer comprising a promoter sequence for an RNA polymerase and a sequence complementary to a first strand of said target nucleic acid (Adams et al. teach an amplification primer immobilized to the beads, the primer being complementary to a target nucleic acid (Fig. 1; col. 2, lines 4-25; col. 3, lines 41-62).; and

a labeled hybridization probe immobilized to said surface,

wherein said labeled hybridization probe comprises a sequence complementary to an amplicon synthesized using said amplification primer and said target nucleic acid as a template in a nucleic acid amplification reaction, and

wherein prior to contact of said device with any nucleotide polymerizing enzyme said labeled hybridization probe comprises a detectable label and is immobilized to said surface (Adams et al. teach detection of the amplicons with labeled hybridization probes (col. 4, lines 57-67); col. 13, lines 8-16). Therefore, since the probe is hybridized to an immobilized amplicon, the probe is itself immobilized, according to Applicant's definition. The probe is labeled independently of the polymerization reaction being performed.).

Regarding claim 45, Adams et al. teach glass and plastic (col. 7, lines 45-51; col. 14, lines 36-44).

Regarding claims 46-48, Adams et al. teach covalent immobilization of primers (col. 2, lines 1-3).

Regarding claim 50, Adams et al. teach multiplex detection of different targets using primers with different sequences (col. 5, lines 3-13).

Regarding claims 51 and 52, Adams et al. teach immobilization of a single primer on the solid support (col. 2, lines 1-63; col. 5, lines 7-9; col. 22, lines 48-56; col. 23, lines 19-26).

B) Adams et al. probes binding to an immobilized amplicon, but do not teach immobilized labeled probes.

C) Whitcombe et al. teach amplification of target nucleic acids using primers which also serve as detection probes, where the probe part contains a fluorophore and a quencher (Fig. 1; page 804, paragraphs 5-7; page 805, first and second paragraphs).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the Scorpion primer of Whitcombe et al. in the amplification device of Adams et al. as one of primers. The motivation to do so, provided by Whitcombe et al., would have been, as stated by Whitcombe et al. (page 804, fourth paragraph):

"There are several consequences of this difference in probe–amplicon interaction. In particular, the appearance of signal is rapid and reliable, because probe–target binding is kinetically favored over duplex reannealing and thermodynamically favored over intrastrand secondary structures. The speed of these unimolecular binding events makes this signaling technology highly suitable for rapid assays in which equilibration times are short, giving it an advantage over bimolecular methods in which the rate of the PCR is reduced[14,15].", and (page 805, fourth and fifth paragraphs):

"The method works well for the detection of amplicon (Fig. 2A): large fluorescence increases were observed in the presence of amplicon, but not in the unamplified controls. Furthermore, the detection was highly specific, down to the level of single base changes. The use of

stems in the probe element offers two advantages: first, background signals are minimal because signals from unincorporated Scorpions primers are switched off; second, the stem can be designed to be thermodynamically favored over the binding of probe to mismatch target. The allele-specific hybridization approach was extended to other allelic ratios, and we found that the magnitude of the allele-specific signal was proportional to the relative copy numbers of the variants (Fig. 2B).

The interaction between probe and target is efficient (see Fig. 3). Identical probe and amplicon sequences showed very different characteristics in a real-time assay. The bimolecular version of the assay did produce increased fluorescence, but the unimolecular version was much stronger (>20-fold)."

D) Adams et al. teach amplification of RNA targets (col. 8, lines 3-5), but do not specifically teach amplification using primers comprising a promoter for RNA polymerase, T7 RNA polymerase or reverse transcriptase.

E) Mueller et al. teach amplification of RNA targets using a self-sustained sequence replication method (3SR), which uses a primer containing a T7 polymerase promoter, T7 RNA polymerase and AMV reverse transcriptase (Fig. 1; page 432, third paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art to have used the 3SR reagents of Mueller et al. in the device of Adams et al. and Whitcombe et al. The motivation to do, provided by Mueller et al., would have been, as stated on page 432, last paragraph and page 433, first and second paragraphs:

"Despite its complexity at the molecular level, the 3SR reaction is simple to perform since all enzymes can be added in a single step to a single reaction mixture at a constant temperature. There is no need for a thermocycler or for heat stable enzymes and, since there are no denaturing

conditions, there is no need to add fresh enzymes. (For additional comments comparing PCR to 3SR see Lown 1993.)

Regarding reaction kinetics, the rate of amplification with 3SR is extremely fast in comparison to PCR, especially in the early phases of the reaction. HIV viral RNA has been found to multiply 12 copies to 1010 copies in 90 min by in vitro 3SR (Bush et al. 1992). Another study showed that, while PCR required 85 min to amplify a template 105 times, 3SR can reach the same level of amplification in 15 min (Guatelli et al. 1990). This rapid rate of amplification means that the incubation time for the 3SR reaction can be quite short, usually only 1–2 h."

7. Claim 53 is rejected under 35 U.S.C. 103(a) as being unpatentable over Adams et al. (U.S. patent No. 6,060,288 A; cited in the previous office action), Whitcombe et al. (Nature Biotechn., vol. 17, pp. 804-807, 1999; cited in the previous office action) and Mueller et al. (Histochem. Cell Biol., vol. 108, pp. 431–437, 1997; cited in the previous office action), as applied to claim 44 above, and further in view of Hanninen et al. (U. S. Patent No. 6,310,354 B1).

A) Teachings of Adams et al., Whitcombe et al. and Mueller et al. are presented above

Regarding claim 53, Adams et al. teach kits comprising supports and oligonucleotides (col. 6, lines 9-36), and control nucleic acids (col. 5, lines 32-35), but do not teach oligonucleotide primer which is not immobilized to the surface.

B) Hanninen et al. teach detection of amplification reaction products in solution using primers or probes immobilized to a microparticles and soluble primers (col. 4, lines 23-67; col. 5, lines 1-42).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used one soluble primer in addition to an immobilized primer of Hanninen et al.

in the device of Adams et al., Whitcombe et al. and Mueller et al. The motivation to do so, provided by Hanninen et al., would have been that, as stated by Hanninen et al. (col. 7, lines 38-50):

"The use of monodispersive microparticles as the solid phase in this nucleic acid amplification assay ensures a rapid cycling of the amplification reaction. Since in the reaction, which occurs on the surface of the microparticles, the average distance between the reaction components is very small, the reaction equilibrium is reached quickly. If one of the reaction primers is attached to the microparticle surface the reaction rate in the early stages of the amplification can be further enhanced by the use of a limited unbound supply of the same primer; as the exponential process advances the free primer is exhausted and the primers from the microparticle surfaces replace their function, preferably at the detection limit of the measuring system."

8. No claims are allowed.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Teresa E. Strzelecka whose telephone number is (571) 272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
Art Unit 1637

Teresa Strzelecka
10/27/06